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Movement restriction does not modulate sensory and perceptual effects of exercise-induced arm pain

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Keywords Delayed onset muscle soreness, DOMS, acute pain, movement restriction, left/right judgements, pressure pain, sensory function, tactile acuity

Abbreviations

| | |
|------------|------------------------------------|
| ANOVA | Analysis of Variance |
| DOMS | Delayed onset muscle soreness |
| η^2 | Eta-squared |
| CRPS | Complex regional pain syndrome |
| LBP | Low back pain |
| <u>LLR</u> | <u>Limb laterality recognition</u> |
| MDT | Mechanical detection threshold |
| 1RM | One repetition maximum |
| PASS-20 | Pain anxiety symptoms scale |
| PPT | Pressure pain threshold |
| TPD | Two-point discrimination |
| VAS | Visual analogue scale |
| SD | Standard deviation |

ABSTRACT

Background Movement restriction has been proposed as an important modulator of changes in sensory and perceptual function and motor imagery performance that are observed in musculoskeletal pain syndromes. There are no empirical data to support this view.

Purpose The primary objective of this experiment was to determine the effects of movement restriction on local and widespread sensory, perceptual and motor imagery changes after exercise-induced muscular pain. Further objectives were to investigate whether changes in basic sensory perception are correlated with pain intensity and tactile acuity or motor imagery performance.

Methods In forty healthy volunteers, delayed onset muscle soreness (DOMS) of the non-dominant elbow-flexors was induced using eccentric contractions until exhaustion. Participants were then randomised into two groups: a movement restriction group (wearing a sling) or a control group (not wearing a sling). Sensory and perceptual function was measured using a range of sensory tests and a motor imagery performance task (left/right limb judgements).

Results Movement restriction did not modulate any of the measures. We found concurrent mechanical hypoesthesia ($p < 0.01$), reduced tactile acuity ($p = 0.02$), and pressure hyperalgesia ($p < 0.01$) at the painful side. We found evidence of widespread pressure hyperalgesia. Impaired tactile acuity was associated with a decrease in pain threshold to pressure ($r = -0.34$, $p = 0.03$). Motor imagery performance was unchanged ($p > 0.35$) by pain or movement restriction.

Conclusion Short-term movement restriction did not influence local and widespread sensory changes induced by experimentally induced muscular pain.

Introduction

There is considerable evidence that ongoing pain is characterised by altered sensory and perceptual function of the painful body part (Passatore and Roatta 2006; Rakel et al. 2014, Sumitani et al. 2007; Valencia et al. 2011). This includes alterations in sensory perception, such as increased perceptual and decreased pain thresholds (Chien et al. 2008; Kavchak et al. 2012; Puta et al. 2013), as well as deficits in tactile acuity (i.e. the smallest distance between two points at which a person can tell that they are being touched by two points and not one) (Catley et al. 2014; Luomajoki and Moseley 2011; Moseley 2008; Stanton et al. 2013; Wand et al. 2010). Evidence also suggests disruptions in motor imagery performance (i.e. the mental execution of a movement) (Bowering et al. 2014; Moseley 2008; Stanton et al. 2012), considered a surrogate measure of cortical proprioceptive representation (Wallwork et al. 2013a; Wallwork et al. 2013b; and see Moseley and Flor 2012; Moseley et al. 2012; Wand et al. 2011 for reviews).

The mechanisms underlying these sensory and perceptual changes are largely unknown. It is uncertain, for example, whether sensory and perceptual changes are present before pain, occur after pain onset, or develop as pain persists (Hübscher et al. 2014; O'Neill et al. 2011). Their contribution to clinical symptoms is also not well understood. In shoulder pain, participants' sensitivity to a suprathreshold heat stimulus is associated with clinical pain intensity (Valencia et al. 2011). However, in participants with chronic low back pain (LBP) or knee osteoarthritis, tactile acuity and motor imagery performance, were not related to pain duration or intensity (Stanton et al. 2013; Wand et al. 2010).

One variable that might prove to be important in linking sensory and perceptual changes to pain is movement restriction. The clinical group in which these changes appear most striking is complex regional pain syndrome (CRPS), a condition almost always preceded by a period of post-injury immobilization (Moseley 2004; Pleger et al. 2006). Indeed, cast immobilization following bone fracture is associated with impairments in tactile acuity and reorganization of the sensory and motor cortices (Liepert et al. 1995; Lissek et al. 2009). In healthy volunteers,

forearm cast immobilization alone has shown movement-related pain together with mechanical and cold hyperalgesia (Terkelsen et al. 2009) as well as reductions in the magnitude of capsaicin-induced pain (Terkelsen et al. 2008).

However, cast wearing involves excessive limb immobilization and therefore, does not adequately reflect clinical pain conditions such as radiating neck pain, lateral epicondylitis, or shoulder pain, in which movement of the painful body part is merely restricted. In order to explore this issue, it is important to be able to differentiate the effects of movement restriction from those of pain or injury. To ascertain the effects of movement restriction, we first used the established method of exercise-induced delayed onset muscle soreness (DOMS) of the elbow flexors (Chen et al. 2013; Hübscher et al. 2008), and then followed it by sling movement restriction or no sling movement restriction. DOMS invokes mechanical allodynia/hyperalgesia that involves peripheral (Binderup et al. 2010; Nie et al. 2006) and, possibly, central sensitization (Nie et al. 2006), is felt deep in the affected area and is sensitive to mechanical input, characteristics it has in common with many clinical pain states.

The primary hypothesis was that DOMS with movement restriction would cause greater local and widespread sensory and perceptual changes than DOMS without movement restriction. The secondary hypothesis was that the magnitude of sensory changes, perceptual changes and pain intensity would be positively related.

Methods

Study design and randomization

This study was a two arm, randomised repeated measures experiment. Participants attended the research laboratory on two occasions (Day 1 and Day 3). On Day 1 completed a questionnaire that included descriptive information, i.e. sex, age, weight and height, a short-form pain anxiety symptoms scale (PASS-20) questionnaire and we obtained baseline

measures on the outcome variables (see below). Upon completion of all assessments, participants undertook the DOMS induction protocol. The researcher then opened the randomisation (computer generated random number table) envelope and the participant was allocated into either the Movement Restriction Group, where they were asked to wear a sling on their experimental arm, or to a Control Group, where they could move their arm freely. Participants in the movement restriction group were asked to wear the sling 'as much as possible between now and the follow-up session', which occurred on Day 3, 48 hours later. Pain intensity was re-assessed at 24 hours and all measures were reassessed at 48 hours (at the laboratory). All assessments were performed by an investigator who was blinded to group. All sensory-perceptual tests were performed by an investigator blinded to the subject's PASS-20 and pain intensity ratings. To ensure blinding, participants were advised to take off the sling before entering the research facility and not to disclose their group allocation to the assessor.

Compliance

Compliance with daily wearing of the sling was assessed by a self-report diary. In response to the question 'For how long did you wear the sling today?', participants selected one of the following responses: less than 4 hours; 4-8 hours; 8-15 hours; 15-20 hours; more than 20 hours. If they selected 'less than 4 hours', they were asked to specify the wearing time in hours.

Participants

Participants were recruited from staff and students at the University of New South Wales and Neuroscience Research Australia through local and online advertisements. They were included if they were aged between 18-50 years and had no current major medical diseases. Participants were excluded from the study if they had any current pain, had taken pain-

relieving medications in the previous 48 hours, had any known contraindications to the exercise protocol (e.g. asthma), had previous surgery in the arms or shoulders or had a history of neurological illness. Participants were advised to not take pain-relieving medication or use any form of pain management (e.g. heat and ice packs), during the 48 hour experimental period. Our a priori sample size calculation was performed by the algorithm given in G*Power 3 for repeated measures analysis of variance (ANOVA; within-between interaction) (Faul et al. 2007). Assuming a two-sided significance level of 5% and correlation between repeated measurements of $\rho=0.4$, a sample size of 40 would have an 80% chance of detecting effects of medium size ($f = 0.25$). Presuming no drop-outs, 40 participants were recruited into the study. All participants gave written informed consent and the protocol was approved by the institutional human ethics committee. Participants received an AU\$40 reimbursement for their participation.

Outcomes

Pain intensity during the last 24 hours, at rest and during movement, was assessed with visual analogue scales (VAS) in response to the questions “Indicate on the scale below the average pain intensity in your arm over the last 24 hours” and “Indicate on the scale below the intensity of the pain in your arm when you move it”. The VAS was anchored at left with “no pain” (score of 0) and at right with “worst pain imaginable” (score of 10 [10-cm scale]).

Sensory and perceptual measures were: mechanical detection threshold (MDT); pressure pain threshold (PPT); two-point discrimination (TPD) threshold; left/right hand judgements. MDT, PPT, and TPD threshold were assessed bilaterally over the medial aspect of the biceps brachii muscle belly, at the midlevel of the arm.

Mechanical detection threshold (MDT): A set of von Frey filaments (MARSTOCK^{nerve}test, Fruhstorfer, Maburg Germany) that exert forces upon bending from 0.25 to 100 mN was used to measure the sensory threshold of light touch (Rolke et al. 2006a; Rolke et al. 2006b). Force was gradually increased until the filament bent and participants were

instructed to indicate when the stimulus was detected. The force was increased or decreased following a negative or positive response respectively, and the mean of five threshold determinations was used for analysis. To ensure blinding of participants, a wooden partition was used to obstruct their view during application of the filaments.

Pressure pain threshold (PPT): PPT was defined as the minimum amount of force required to elicit pain, as distinct from pressure or discomfort. A pressure algometer (Wagner Instruments, Greenwich, USA) was used to apply pressure at a rate of 5N/s until the subject reported pain. (Fischer 1987). At this point, the force value (Newton) was recorded as the PPT. The mean of three trials was used for analysis.

Two-point discrimination (TPD) threshold: TPD threshold was assessed (Catley et al. 2013; Moberg 1990; Seltzer and Seltzer 1986) using digital calipers (Sontax, Perth, Australia). TPD threshold was defined as the shortest distance between caliper points at which participants could clearly detect two points instead of one. In each participant one ascending and one descending run were completed (using 5mm increments). The order of runs was randomised. The average TPD threshold obtained in these two runs was used to calculate the TPD threshold.

Motor imagery: Left/right hand judgements: Seated participants undertook a left/right hand judgement task using photographs of the left and right hand displayed in random order on a monitor (Recognise Software, Neuro Orthopaedic Institute, Adelaide, Australia; <http://www.noigroup.com>) (Moseley 2006b). Participants responded by pressing the appropriate response keys ('a' for left and 'd' for right) depending on the image shown on the monitor. They were instructed to make accurate responses as quickly as possible. Twenty pictures constituted a trial. Participants completed one practice trial. Data from a second trial were extracted and the mean response time for accuracy responses (RT), and the accuracy of responses (the proportion of responses that were correct) were used for analysis.

Exercise Protocol

DOMS was induced in the elbow flexors of the non-dominant arm using a dumbbell and standard eccentric loading protocol (Hübscher et al. 2008). The experimenter lifted the predetermined weight (i.e. one repetition maximum, 1RM; the maximum weight participants could concentrically lift once) to the point of maximum elbow flexion and participants then lowered the weight to full elbow extension. They were advised, and practiced beforehand, to use a smooth controlled movement at a speed that would take three seconds to move from full flexion to full extension. This pattern was repeated until exhaustion. A 30-second rest interval was then given and the procedure (to exhaustion) was repeated three times.

Statistical Analysis

An independent t-test tested for group differences in the PASS-20 score.

The effect of movement restriction after DOMS induction on pain intensity was assessed using a two (Factor Group: Movement Restriction or Control) x three (Factor Time: pre-DOMS, 24 hours, or 48 hours) repeated measures ANOVA. The effects on our other outcome variables were assessed using a two (Factor Group: Movement Restriction or Control) x two (Factor Time: Pre-DOMS or 48 hours) repeated measures ANOVA (Model 1).

To ascertain whether potential effects were restricted to the DOMS affected side, we used a two (Factor Side: Experimental or Control) x two (Factor Time: Pre-DOMS or 48 hours) repeated measures ANOVA (Model 2). To conclude that any effects were specific to the exercised arm, we required a Side x Time interaction.

Estimates of effect sizes were based on partial Eta-squared (η^2). Partial η^2 describes the proportion of total variance attributable to a factor (main or interaction effect), excluding variance explained by other factors and ranges from 0 to 1 (Pierce et al. 2004).

For our secondary hypotheses, Pearson's correlations coefficients (r) were calculated between pain intensity and the sensory (MDT, PPT, TPD threshold) changes, and between changes in TPD threshold and MDT, and TPD threshold and PPT. As a guideline, the

following cut-off points were used to interpret the strength of the relationship: little or none (0.00 to 0.25), fair (0.25 to 0.50), moderate to good (0.50 to 0.75), and good to excellent (above 0.75) (Portney 2009).

If diary-based compliance data were not available for all participants, we used an independent t-test to compare 48 hour data for all outcome variables between those participants for whom sling wearing compliance data were available and those for whom it was not.

Significance was set at $\alpha=0.05$. Multiple comparisons adjustments were made with Bonferroni–Holm correction. All statistical analyses were performed using SPSS 22.0 for Windows (IBM, Armonk, NY, USA).

Results

Forty healthy volunteers (Control Group (n =20): mean (SD) age = 26 (5) years; Movement Restriction Group (n =20): 25 (8) were included. PASS-20 scores were not significantly different between groups (37.25 (17.17) for the Control Group; 28.95 (12.55) for the Movement Restriction Group; p =0.09).

Data on compliance with wearing the sling (Table 1) were available from 10 participants (missing data due to data entry error). There was no significant difference in any of the outcome variables at 48 hours between participants for whom sling wearing compliance data were available and those for whom it was not (p >0.5 for all).

Pain intensity was greater at 24 and 48 hours than it was at pre-exercise (Fig. 1, Table 2). PPT was lower, and MDT and TPD threshold were higher, at 48 hours than at pre-exercise (Table 2). However, movement restriction did not modulate any of the primary outcome variables. That is, the repeated measures ANOVA (model 1) showed significant main effects of Time for pain intensity at rest ($F(2, 37)=44.23$, $p<0.01$, partial $\eta^2=0.71$) and during

movement ($F(2, 37)=61.58, p<0.01, \text{partial } \eta^2=0.77$), MDT ($F(1, 38)=24.30, p<0.01, \text{partial } \eta^2=0.40$) (Fig.1, Table 2), PPT ($F(1, 38)=26.68, p<0.01, \text{partial } \eta^2=0.43$), and TPD threshold ($F(1, 38)=5.73, p=0.02, \text{partial } \eta^2=0.45$) (Table 2). The interactions between group and Time for pain intensity at rest ($F(2, 37)=0.24, p=0.79$), pain intensity during movement ($F(2, 37)=0.24, p=0.79$), MDT ($F(1, 38)=0.33, p=0.57$), PPT ($F(1, 38)=1.61, p=0.21$), or TPD threshold ($F(1, 38)=0.37, p=0.55$) were not significant, indicating that DOMS-induced changes did not differ between the groups.

Model 2 showed that the interaction between Time and Side was statistically significant for MDT ($F(1, 39)=22.37, p<0.01$) and TPD ($F(1, 39)=24.87, p<0.01$), indicating that mechanical hypoesthesia and loss of tactile acuity were restricted to the DOMS-affected side (Table 2). For PPT, in contrast, the Time by side interaction was not significant ($F(1, 39)=2.84, p=0.10$), indicating that hyperalgesia also occurred at the contralateral side (Table 2).

Correlation coefficients for the DOMS-affected side are presented in Table 3. Sensory (MDT, PPT, TPD threshold) changes were not correlated with pain intensity, at rest or during movement, at 48 hours. A fair, negative correlation was found between the changes in TPD threshold and PPT ($r=-0.34, p=0.03$), indicating that a loss in tactile acuity was associated with an increase in sensitivity to pressure.

Discussion

Our primary hypothesis that DOMS with movement restriction would cause greater local and widespread sensory and perceptual changes than DOMS without movement restriction was not supported. We found mechanical hypoesthesia (increased MDT), pressure hyperalgesia (reduced PPT) and a loss of tactile acuity (increased TPD threshold) but no change in left/right judgement performance. Surprisingly, there was no added effect of immobilization of the DOMS-affected arm for any of the outcomes. Further, all changes were unilateral and involved only the DOMS-affected arm, with the exception of PPT which also decreased on

the DOMS-affected arm. Our secondary objectives were to evaluate the relationship between sensory and perceptual changes and pain intensity as well as the relationship between changes in tactile acuity and motor imagery performance (TPD threshold and left/right judgements) and changes in sensory perception (MDT and PPT). Contrary to our hypotheses, none of these factors were associated, with the exception of TPD threshold and PPT, suggesting that despite the presence of decreased tactile acuity, sensitivity to pressure stimuli increases.

That we did not find a difference in sensory and perceptual performance between groups (DOMS only versus DOMS plus movement restriction) is in contrast to studies in which patients who have sustained a fracture are subsequently immobilised with a cast. Following hand and arm immobilisation, tactile acuity was lower on the fractured and immobilised side than on the unaffected side, and lower than in healthy controls (not wearing a cast) (Lissek et al. 2009). Similarly, in patients who had their ankle joint immobilized with a splint, there was a decrease in the area of primary motor cortex that evoked a response in the shin muscle (tibialis anterior) on the affected side (Liepert et al. 1995). The magnitude of this reduction in motor cortical representation of tibialis anterior was positively related to the duration of mobilisation. However, such studies cannot isolate the role of immobilisation in imparting these effects. That is, they may reflect sustained nociceptive drive – as has been demonstrated experimentally (Gandevia and Phegan 1999) – and it is clearly problematic to investigate experimentally whether or not immobilisation of the fracture site contributes to the observed effects.

Cast immobilisation without injury has yielded contrasting results. For example, immobilization of the forearm induced transient movement-provoked pain together with mechanical and cold hyperalgesia at the immobilized extremity compared with the non-immobilized side and controls (Terkelsen et al. 2009). On the contrary, in their non-randomized study, Terkelsen et al. (2008) found a delayed onset and diminished magnitude of capsaicin-induced pain after forearm immobilization. That the duration of immobilization in

these studies was 4 weeks suggests that the 3 days immobilization in our study might have been too short to induce changes in pain and/or sensory function. Further, the method and/or extent of movement restriction may be relevant to the differences found between our study and previous studies. One would expect that full immobilisation (cast) versus movement restriction (sling) would have more profound effects on the restricted body part. We avoided cast immobilisation because it is only clinically relevant to fracture and joint dislocation, whereas we wanted to model the much more common situation of movement restriction, for example as occurs in conditions such as lateral epicondylitis or shoulder pain. Intra- and interindividual movement variations in pain, however, present across a spectrum from subtle changes in muscle coordination to partial and/or complete avoidance of certain activities (Hodges and Smeets 2014) and our model can only capture some aspects of these changes.

Our finding of sensory and perceptual changes in the affected forearm, as well as bilateral pressure hyperalgesia, is in agreement with recent experimental pain findings. In healthy volunteers, exercise-induced muscle soreness of the lower back was associated with higher heat-evoked pain ratings over lumbar dermatomes (Bishop et al. 2012). Interestingly, dynamic pain processing, i.e. temporal summation of heat-evoked pain, was associated with pain intensity from DOMS, while responses to single suprathreshold stimuli, i.e. static pain processing, were not. The authors interpreted their results as reflecting upregulation of central nociceptive processing. Our own findings of a lack of association between static measures of sensory and perceptual function and pain intensity, and bilateral pressure hyperalgesia, also seem consistent with changes in central processing. Supraspinal mechanisms that evoke central sensitization might also trigger inhibitory pain modulation (Vo and Drummond 2013). That we found both pressure hyperalgesia and mechanical hypoesthesia is consistent with data from people with back pain, who have reduced pain thresholds but increased mechanical detection thresholds (Agostinho et al. 2009; Chien et al. 2008; Chien et al. 2009).

We did not find a relationship between sensory changes and pain intensity. It is conceivable that numerous other factors, including pain-related psychological and genetic variables, also account for the variability in pain intensity (Hübscher et al. 2013a). A previous study suggested pain catastrophizing and catechol-O-methyltransferase (COMT) genotype predicted pain intensity ratings of participants exercise-induced DOMS at the shoulder (George et al. 2007). However, in our study, exploratory bivariate correlation analyses did not demonstrate a relationship between pain anxiety symptoms (PASS-20) at baseline and pain intensity at 48 hours at rest ($r=0.09$, $P=0.60$) or during movement ($r=0.12$, $P=0.45$).

In addition to the question about the role of central changes in the generation of musculoskeletal pain, the time course of such changes is not known. Even though basic evidence suggests that changes in the central nervous system can occur within hours of injury (Ji et al. 2003; Salter 2004), studies in humans are limited and have found different results. Generalized hyperalgesia has been demonstrated in patients with acute whiplash injury (Sterling et al. 2003), but not in those with acute LBP (O'Neill et al. 2011). However, the present study provides further evidence that, in addition to peripheral sensitization mechanisms, central changes can occur within 48 hours of injury. This assumption is corroborated by previous studies that have demonstrated temporal summation of pain in DOMS, which has been interpreted as a sign of central sensitization (Nie et al. 2006).

Our final objective was to evaluate whether changes in tactile acuity or motor imagery performance, are associated with MDT or PPT. We found that changes in TPD threshold demonstrated a fair correlation with PPT, indicating that a loss of tactile acuity was associated with mechanical hyperalgesia. While speculative, it is possible that functional changes in cortical representation, indicated by the change in TPD (Pleger et al. 2001), can occur early after musculoskeletal injury and may contribute to hyperalgesia. The finding that the reduction of MDT, e.g. local hypoaesthesia, was not correlated with TPD change support our suggestion that the change in tactile acuity is primarily evoked by central processes. However, this hypothesis should be confirmed in future brain imaging studies.

There are limitations that should be acknowledged. We used DOMS as our experimental model because it evokes a perceptual experience that is comparable to that experienced clinically (Brandt et al. 2014; Chien et al. 2008; Kavchak et al. 2012; O'Neill et al. 2007; Stanton et al. 2013). However, DOMS is associated with a particular physiological process and it is possible that the physiological processes that induce sensory and perceptual changes clinically are not captured by the DOMS model. The typical time course of DOMS is characterized by pain and tenderness that peak between 48 and 72 hours, but can endure for up to seven days post-exercise (Cheung et al. 2003; Smith 1991). We planned the experiment so as to capture the likely peak of DOMS, but may therefore have missed effects that emerge later, either because of sustained nociceptive input or related to different stages of healing and recovery. Even though pain intensity ratings with a 24 hours recall period are well-established and have demonstrated adequate psychometric properties (Hawker et al. 2011, Jensen et al. 2008), they can be subject to recall bias. Ratings of current pain intensity on multiple occasions during the day using a pain diary could provide additional value in future studies. Furthermore, participants were asked to wear the sling as long as possible, and compliance was assessed via self-report. This method increases compliance by about 8%, but is also associated with over-estimation of true compliance, by about 10% (Moseley 2006a). It is prudent then to suspect that true compliance was lower than that reported, but, importantly, only about 10% (Moseley 2006a). Future studies should verify our findings, in evoked and spontaneous pain, through measurements of arm movement using validated activity monitors such as the Upper Limb Activity Monitor (ULAM). Activity monitors could also be used in longitudinal patient cohorts to investigate the dose-response relationship between (limb) movement, sensory function, pain, and disability in acute and chronic musculoskeletal pain.

In conclusion, the present study shows both local and widespread sensory changes occur concurrently with the development of pain induced by a standard DOMS protocol. Contrary

to our hypotheses, neither pain nor sensory changes were influenced by movement restriction.

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Conflict of interest None.

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Table Legends

Table 1 Compliance with wearing the sling; data from 10 participants.

^a3 hours.

^bMean (SD): 2 (1) hours.

Table 2 Outcome variables.

All values are means (SD) except for pain at rest/during movement (median \pm interquartile range).

Abbreviations: DOMS: delayed onset muscle soreness; VAS: visual analogue scale; MDT: mechanical detection threshold; PPT: pressure pain threshold; TPD: two point discrimination; LLR: limb laterality recognition.

^aTwo-way repeated measures ANOVA, significant main effect of time, $P < 0.01$.

^bTwo-way repeated measures ANOVA, significant time by site interaction, $P < 0.01$.

Table 3. Correlation coefficients.

Abbreviations: VAS: visual analogue scale; MDT: mechanical detection threshold; PPT: pressure pain threshold; TPD: two point discrimination.

^a $p < 0.05$

^b $p < 0.01$

Figure Legends

Fig. 1 Mean absolute changes in pain intensity over time. Pain intensity during the last 24 hours, (a) at rest and (b) during movement, was assessed with visual analogue scales ranging from 0-10 (0 = “no pain”, 10 “worst pain imaginable”). Error bars represent standard deviation (SD). Significant main effect of time, $P < 0.01$, two-way repeated measures ANOVA.